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The impact of left ventricular ejection fraction on heart failure patients with pulmonary hypertension

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ABSTRACT

Background: The most common cause of pulmonary hypertension (PH) in developed countries is left heart disease (LHD, group 2 PH). The development of PH in heart failure (HF) patients is indicative of worse outcomes.
Objective: The aim of this study was to evaluate the long term outcomes of HF patients with PH in a national long-term registry.
Methods: Study included 9 cardiology centers across Israel between 01/2013–01/2015, with a 12-month clinical follow-up and 24-month mortality follow-up. Patients were age ≥18 years old with HF and pre-inclusion PH due to left heart disease determined by echocardiography [estimated systolic pulmonary arterial pressure (SPAP) ≥ 50 mmHg]. Patients were categorized into 3 groups: HF with reduced (HFrEF < 40%), mid-range (HFmrEF 40–49%), and preserved (HFpEF ≥ 50%) ejection fraction.
Results: The registry included 372 patients, with high prevalence of cardiovascular risk factors. Median HF duration was 4 years and 65% were in severe HF New York Heart Association (NYHA) classification ≥3. Mean systolic pulmonary artery pressure (SPAP) was 62 ± 11 mmHg. During 2-years of follow-up, 54 patients (15%) died. Univariable predictors of mortality included NYHA grade 3–4, chronic renal failure, and SPAP ≥ 65 mmHg. Severe PH was associated with mortality in HFpEF, but not HFmrEF or HFrEF, and remained significant after multivariable adjustment with an adjusted hazard ratio of 2.99, (95%CI 1.29–6.91, $p = 0.010$).
Conclusions: The combination of HFpEF with severe PH was independently associated with increased mortality. Currently, HFpEF patients are included with group 2 PH patients. Defining HFpEF with severe PH as a sub-class may be more appropriate, as these patients are at increased risk and deserve special consideration.

Introduction

Pulmonary hypertension secondary to left heart disease (PH-LHD; group 2 PH) is defined as a mean pulmonary artery pressure (PAP) ≥ 25 mmHg and a pulmonary artery wedge pressure (PAWP)

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> 15 mmHg[1] PH-LHD leads to retrograde transmission of elevated filling pressures, mainly driven by left ventricular diastolic or systolic dysfunction.[2,3] This sustained elevation of pressure leads to pulmonary capillary stress failure, arterial remodeling, impaired vascular reactivity and endothelial dysfunction, which are similar to the changes seen in group 1 PH.[4]

Multiple studies have established that development of PH in patients with heart failure (HF) with preserved ejection fraction (HFpEF) is indicative of worse outcomes.[5,6] Data from these studies put the prevalence of PH-LHD between 25% and 79% in patients with HFpEF and HF with reduced ejection fraction (HFrEF).[7,8] Given the extremely high prevalence of HF in the general population, perhaps the most common cause of PH is LHD (group 2 PH). The purpose of this study was to investigate the characteristics and prognosis of HF patients with PH in a national long-term registry, within the 3 subtypes of HF defined by left ventricular ejection fraction (EF), including baseline characteristics, comorbidities, renal and heart status, and pulmonary hypertension.

Methods

Study design and patient population

The Israeli HF-PH Registry is a prospective, multicenter, observational study of patients presenting to nine cardiology centers in Israel. The centers included in the study were considered representative of the Israeli HF patient population. The Israeli Association for Cardiovascular Trials (I-ACT) coordinated the project and collected the data input from each center, which were transmitted via electronic based case report forms. The enrollment period was between 01/2013–01/2015 with a 12-month follow-up duration on clinical parameters and 24-month follow-up on mortality. The Central Data Coordinating Center (based at the Sheba Medical Center) was responsible for the collection of all case report forms. Two-year mortality rates were ascertained by use of the Israeli National Population Registry.

Inclusion criteria were: patient's age ≥18 years with a clinical diagnosis of HF with evidence of World Health Organization group 2 PH (defined as due to left heart disease) followed in a specialized cardiovascular center. PH was determined by echocardiography performed within 12 months before inclusion in the study and defined as estimated systolic pulmonary arterial pressure (SPAP) ≥ 50 mmHg.[9-11] Patients with other etiologies of PH were excluded (i.e. pulmonary arterial hypertension [group 1], due to lung diseases and/or hypoxemia [group 3], thromboembolic pulmonary disease [group 4] or congenital heart disease,[1] including ventricular septal defect, atrial septal defect, patent ductus arteriosus, Ebstein's anomaly, or Eisenmenger's syndrome).

Biochemical blood measurements of hemoglobin, creatinine, sodium, and potassium were determined using local standard laboratory procedures. Conventional trans-thoracic echocardiograms were used to measure left ventricular ejection fraction and (SPAP) according to international standard criteria.[9,10] Patients were categorized into 3 groups: HF with reduced (HFrEF < 40%), mid-range (HFmrEF 40–49%), and preserved (HFpEF ≥ 50%) ejection fraction.[11]

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 20.0 and MEDCALC version 16.8). Continuous data are presented as mean ± standard deviation or median with interquartile range (IQR) and categorical variables as numbers and percentages. Analysis of variance or independent samples t-tests were used to compare continuous variables and Chi-square to compare categorical variables. The Fisher exact test was used in case of small sample size. Univariable and multivariable Cox regression analyses were used to estimate the association between baseline characteristics and 2-year mortality in HF patients with PH, calculating adjusted hazard ratios (HR) and 95% confidence intervals (CI). Included in the multivariable model were variables with a significance level <0.20 in the Univariable analysis. One-year and 2-year survival rates in relation to PH severity and ejection fraction subtypes were calculated, using the Kaplan-Meier method, and statistical comparison performed, using the log-rank test. Multivariable analysis of the association of PH severity across HF ejection fraction subtypes with mortality was performed, using the Cox proportional hazards model with forward stepwise selection of covariates. Included in the models were variables with clinical significance including baseline characteristics (age and sex); comorbidities (diabetes mellitus, coronary artery disease [CAD]); chronic renal failure defined as baseline creatinine > 1.4 (mg/dL); heart failure status (New York Heart Association functional class); and ischemic cardiomyopathy. Prognostic significance of SPAP was evaluated by comparing the highest tertile to the lower 2 tertiles. Youden's Index was calculated from the receiver operating characteristic (ROC) curve to find an optimal threshold value of SPAP in discrimination of 2-year mortality. The results were considered statistically significant when the 2-sided *p*-value was <0.05. The study was approved by each local institutional ethical review board. No data were collected for the study purposes before a signed informed consent was obtained.

Results

The PH-HF registry included 397 patients; of them, 372 had available echocardiographic data, forming the final study cohort.

Characteristics of overall study patient population

Baseline characteristics of the overall HF-PH study population in relation to EF subtypes are presented in Table 1a and Table 1b. Patients were in the 8th decade of life, with high prevalence of cardiovascular risk factors, including hypertension, hyperlipidemia and diabetes. Half had previous history of CAD, 80% of whom presented with myocardial infarction. HF symptoms were present for a median of 4 years prior to enrollment (range 1–10 years), and 65% of patients had severe HF (NYHA 3–4). Jugular venous distention, pulmonary congestion and pedal edema were common, while hepatomegaly and ascites were rather rare. Hemodynamically, blood pressure and heart rate were in the normal range, yet SPAP was severely elevated. Left ventricle mass and left atrial systolic dimension indices were increased. Creatinine ≥ 1.4 mg/dl was present in 40% of patients. Serum electrolytes and hemoglobin were within normal ranges. Medication reflected guideline endorsed therapy for background disease and risk factors, as indicated in Table 1b.

Characteristics of the EF subgroups

HFpEF was more commonly associated with female sex, older age, obesity and diagnosis of atrial fibrillation, while HFrEF was more commonly associated with CAD, renal failure, smoking, higher rates of HF admissions and more prolonged duration of HF. In addition, jugular venous distention, lower systolic blood pressure, higher resting heart rate, as well as wider QRS segment on electrocardiogram, were more common in patients with HFrEF. The prevalence of CAD and previous percutaneous coronary interventions was identical in patients with HFmrEF and HFrEF, and twice as common compared to HFpEF. The prevalence of other baseline characteristics in HFmrEF was intermediate between the other two HF EF subtypes in some parameters, but did not show any consistent pattern (Tables 1a–1b). Mean SPAP of the overall study population was 62 ± 11 mmHg and did not differ significantly between groups. Left atrial remodeling was observed in all

Table 1a
Clinical characteristics according to heart failure ejection fraction subtypes

Variable	Total (n = 372)	HFrEF (n = 159)	HFmrEF (n = 50)	HFpEF (n = 163)	P value
Gender (male)	210 (56)	125 (79)	34 (68)	51 (31)	<**0.001**
Age	77.3 ± 10.3	74.4 ± 10.8	79.0 ± 8.1	79.7 ± 9.8	<**0.001**
Diabetes Mellitus	205 (55)	93 (58)	29 (58)	83 (51)	0.357
Hyperlipidemia	277 (75)	122 (77)	41 (82)	114 (70)	0.159
Hypertension	316 (85)	137 (86)	41 (82)	138 (85)	0.766
Current smoker	36 (10)	22 (14)	5 (10)	9 (6)	**0.041**
PVD	36 (10)	15 (9)	7 (14)	14 (9)	0.522
Obesity	174 (47)	62 (39)	24 (48)	88 (54)	**0.026**
BMI*	30.5 ± 6.5	29.0 ± 5.5	30.6 ± 7.0	31.7±.9	**0.005**
CAD	186 (50)	98 (62)	31 (62)	57 (35)	<**0.001**
Past myocardial infarction	149 (40)	96 (60)	21 (42)	32 (20)	<**0.001**
Past valve surgery	66 (18)	23 (14)	10 (20)	33 (20)	0.366
Past PCI	178 (48)	96 (60)	30 (60)	52 (32)	<**0.001**
Past CVA/TIA	51 (14)	18 (11)	7 (14)	26 (16)	0.481
Past oncologic disease	42 (11)	21 (13)	6 (12)	15 (9)	0.517
Past HF admissions	201 (54)	101 (64)	24 (48)	76 (47)	**0.021**
HF duration	6.5 ± 7.4 4 (1–10)	7.7 ± 7.4 6 (2–11)	6.9 ± 7.9 5 (1–10)	5.1 ± 7.1 3 (1–8)	**0.006**
NYHA 3–4	243 (65)	114 (72)	26 (52)	103 (63)	**0.029**
Ischemic cardiomyopathy	173 (46)	112 (70)	25 (50)	36 (22)	<**0.001**
Atrial Fibrillation	83 (22)	21 (13)	11 (22)	51 (31)	<**0.001**
QRS width > 130 mm	154 (41)	83 (52)	22 (44)	49 (30)	<**0.001**
Device therapy	138 (37)	104 (65)	11 (22)	23 (14)	<**0.001**
ICD/CRTD	98 (26)	90 (57)	5 (10)	3 (2)	<**0.001**

Data are presented as n (%), mean ± standard deviation (SD), or median and interquartile range (IQR). BMI, body mass index* was available for 281 patients; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; CVA, cerebrovascular accident; HF, heart failure, ICD, implantable cardioverter defibrillator; NYHA, New-York heart association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischemic attack; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction.

subgroups to a similarly large left atrial systolic dimension, while mean left ventricular mass index was at upper normal range for HFpEF and HFmrEF and significantly higher for HFrEF.

Mortality in relation to EF-SPAP

Patients were classified according to SPAP tertiles. The highest tertile (SPAP ≥ 65 mmHg) was considered the cutoff for severe PH, and was analyzed compared to the lower 2 tertiles. The threshold of 65 mmHg was also the optimal value of SPAP to discriminate 2-year mortality in the overall population (sensitivity 46%, specificity 68%).

During 2-years of follow-up, 54patients died (15%). In the overall HF-PH population, reduced functional class (NYHA 3–4), chronic renal failure and severe PH were each associated with elevated 2-year mortality in the univariable analysis (Table 2). However, in a multivariable model, PH severity did not remain an independent predictor for mortality, in contrast to NYHA functional class 3–4 (HR 2.41, 95%CI 1.17–4.97, p = 0.017) and renal failure (HR 2.53, 95%CI 1.45–4.42), p = 0.001).

Kaplan-Meier survival curves for analyzing the prognostic impact of severe PH separately in each of the three HF EF subtypes is presented in Fig. 1a and c, demonstrating an association between severe PH and mortality in HFpEF but not in HFmrEF or HFrEF respectively, with a significant 1- and 2-year corresponding log-rank p-value. The association between PH severity and mortality in patients with HFpEF remained significant after multivariable adjustment for age, sex, heart failure duration, NYHA functional class, creatinine level, diabetes mellitus, CAD and ischemic cardiomyopathy (adjusted HR 2.99, 95%CI 1.29–6.91, p = 0.010) (Fig. 2).

Table 1b
Heart failure manifestations, laboratory and drug therapy, according to heart failure ejection fraction subtypes

Variable	Total (n = 372)	HFrEF (n = 159)	HFmrEF (n = 50)	HFpEF (n = 163)	P value
Heart failure manifestations					
Jugular venous distension	194 (52)	98 (62)	22 (44)	74 (45)	**0.006**
Hepatomegaly	40 (11)	18 (11)	2 (4)	20 (12)	0.167
Pulmonary congestion	102 (27)	49 (31)	16 (32)	37 (23)	0.316
Ascites	36 (10)	23 (14)	0	13 (8)	**0.012**
Pedal edema	175 (47)	80 (50)	23 (46)	72 (44)	0.196
Pleural effusion	56 (15)	30 (19)	4 (8)	22 (14)	0.230
Hemodynamic/ Echocardiographic Parameters					
Systolic BP (mmHg)	130 ± 20	123 ± 20	134 ± 15	135 ± 21	<**0.001**
Diastolic BP (mmHg)	68 ± 13	69 ± 13	68 ± 11	68 ± 13	0.769
Heart rate (bpm)	72 ± 14	74 ± 14	69 ± 12	71 ± 14	**0.034**
SPAP (mmHg)	62 ± 11	61 ± 9	64 ± 14	63 ± 12	0.197
LV mass (gr, n = 218)	220 ± 83	250 ± 96	208 ± 67	192 ± 58	<0.001
LV mass index (gr/m^3, n = 177)	117 ± 44	131 ± 57	110 ± 29	106 ± 29	0.002
LAs dimeter (mm, n = 278)	46.5 ± 8.1	47.9 ± 8.8	45.0 ± 8.0	45.4 ± 7.1	0.026
LAs dimension index (mm/m^3, n = 221)	25.4 ± 5.1	25.3 ± 5.4	25.1 ± 4.7	25.5 ± 4.9	0.936
Tricuspid regurgitation moderate - severe	215 (58)	98 (62)	27 (54)	90 (55)	0.427
Mitral regurgitation moderate - severe	176 (47)	101 (63)	20 (40)	55 (34)	<0.001
Laboratory Test Results					
Hemoglobin (gr/dl)	12 ± 2	12 ± 2	12 ± 2	12 ± 2	0.526
Creatinine ≥ 1.4 mg/dl	147 (40)	82 (51)	19 (38)	46 (28)	<**0.001**
Sodium (mEq/l)	139 ± 3	138 ± 4	139 ± 3	139 ± 3	0.731
Potassium (mEq/l)	4.3 ± 0.6	4.5 ± 0.7	4.6 ± 0.6	4.3 ± 0.6	**0.005**
Medications					
Aspirin	181 (49)	87 (55)	27 (54)	67 (41)	**0.036**
Aldosterone antagonists	138 (37)	74 (46)	13 (26)	51 (31)	**0.004**
ACEI	148 (40)	68 (43)	23 (46)	57 (35)	0.226
ARB	92 (25)	42 (26)	12 (24)	38 (23)	0.805
Statins	225 (68)	119 (75)	37 (74)	99 (61)	**0.016**
Beta-blockers	313 (84)	145 (91)	43 (86)	125 (77)	**0.005**
Furosemide	302 (81)	141 (89)	36 (72)	125 (77)	**0.005**
Nitrates	65 (17)	28 (18)	9 (18)	28 (17)	0.989

Data are presented as n (%) or mean ± standard deviation (SD). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LV, left ventricle; SPAP, systolic pulmonary artery pressure.

Discussion

The main finding of our study is the heterogeneous association of group-2 PH with mortality. While the severity of PH was not related to mortality in the whole HF group per se, it was independently associated with it in the HFpEF sub-group (i.e. left ventricular function ≥ 50%). Specifically, the combination of HFpEF with SPAP ≥ 65 mmHg was significantly associated with increased mortality.

Of note, baseline demographic, clinical parameters and left ventricular systolic function were not related to mortality. Yet, stratifying patients by their left ventricular function did reveal differences in their clinical characteristics as well as in their prognosis in relation to pulmonary pressure. HFpEF was more commonly associated with female sex, older age, obesity and diagnosis of atrial fibrillation, while HFrEF was more commonly associated with CAD, renal failure, smoking, higher rates of HF admissions and more prolonged duration of HF; prevalence of CAD and previous percutaneous coronary intervention (PCI) were identical in patients with HFmrEF and HFrEF, and twice as common compared to HFpEF. Across all EF groups, SPAP was abnormally elevated with evidence in echocardiogram of diastolic dysfunction, commonly accompanied by left atrial remodeling and increased left ventricular mass index.

Table 2
Association between baseline characteristics and 2-year mortality in heart failure patients with pulmonary hypertension

Variable	Univariable HR (95%CI), *p*-Value	Multivariable HR (95%CI), *p*-Value
Gender (male)	1.32 (0.76–2.30), *P* = 0.319	–
Age (years)	1.003 (0.977–1.029), *P* = 0.816	–
Coronary artery disease	1.49 (0.87–2.57), *P* = 0.149	–
Obesity	0.91 (0.53–1.56), *P* = 0.737	–
Diabetes Mellitus	1.04 (0.61–1.78), *P* = 0.890	–
Hypertension	1.77 (0.71–4.44), *P* = 0.223	–
ICDMP	0.91 (0.53–1.56), *P* = 0.737	–
Heart failure duration	1.002 (0.967–1.037), *P* = 0.932	–
NYHA 3–4	**2.86 (1.40–5.84), *P* = 0.004**	**2.41 (1.17–4.97), *P* = 0.017**
Chronic renal failure	**2.86 (1.64–4.97), *P*<0.001**	**2.53 (1.45–4.42), *P* = 0.001**
SPAP ≥ 65 mmHg (T3)	**1.81 (1.06–3.10), *P* = 0.029**	–
HFpEF	1	
HFmrEF	0.75 (0.31–1.83), *P* = 0.530	–
HFrEF	0.90 (0.5–1.58), *P* = 0.710	

HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; ICDMP, ischemic cardiomyopathy; NYHA, New York heart association; SPAP, systolic pulmonary artery pressure.

Mortality in relation to EF-SPAP

The highest SPAP tertile (≥65 mmHg) was found to be the optimal value of SPAP to discriminate 2-year mortality in the overall population. PH severity did not remain an independent predictor for mortality, in contrast to NYHA functional class 3–4 and renal failure. After ejection fraction group stratification, the severity of PH was associated with increased mortality in HFpEF but not in HFmrEF or HFrEF, and this association remained significant in HFpEF after multivariable adjustment for age, sex, heart failure duration, NYHA functional class, creatinine level, diabetes mellitus, CAD and ischemic cardiomyopathy. Importantly, the increased mortality in HFpEF with PH highlights the burden of this disease and the need for further research.

PH is a common finding in patients with HFpEF,[12-15] and it is associated with worse symptoms, reduced exercise capacity, higher natriuretic peptide levels, and increased hospitalization rates and mortality. Older age and PH were the only independent predictors of mortality in a study of 1663 patients with HF and EF ≥ 40%.[16] About a third of patients with HFpEF have evidence of pre-capillary PH as well as the more expected post-capillary PH.[15] Patients with HFpEF and pre-capillary PH were found to be at increased risk for right ventricular failure and death, compared with patients with HFpEF

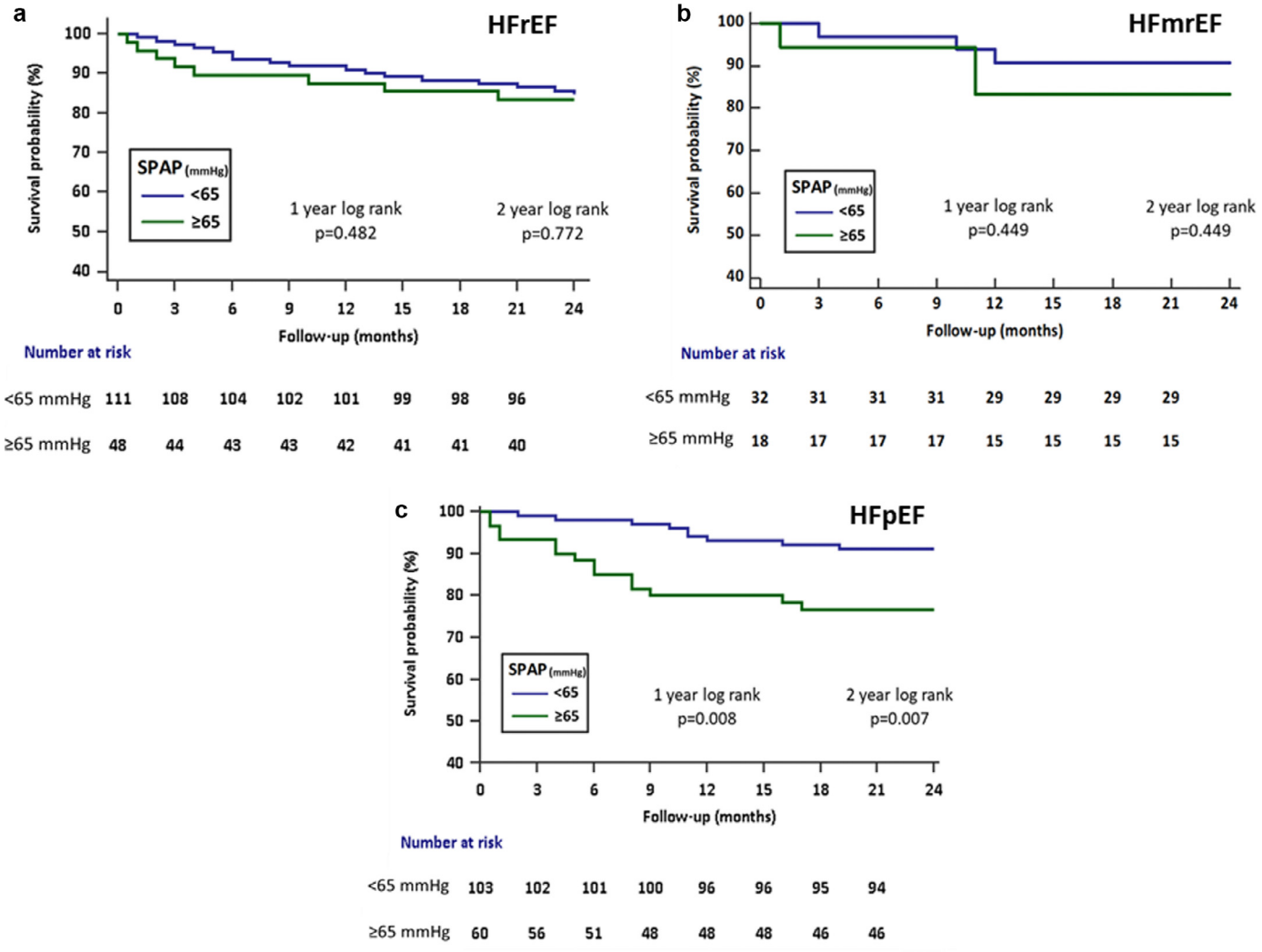

Fig. 1. Two-year survival according to pulmonary hypertension severity and heart failure ejection fraction subtype. 1a. Heart failure with reduced ejection fraction (HFrEF). 1b. Heart failure with mid-range ejection fraction (HFmrEF). 1c. Heart failure with preserved ejection fraction (HFpEF). SPAP, estimated systolic pulmonary artery pressure by echocardiography.

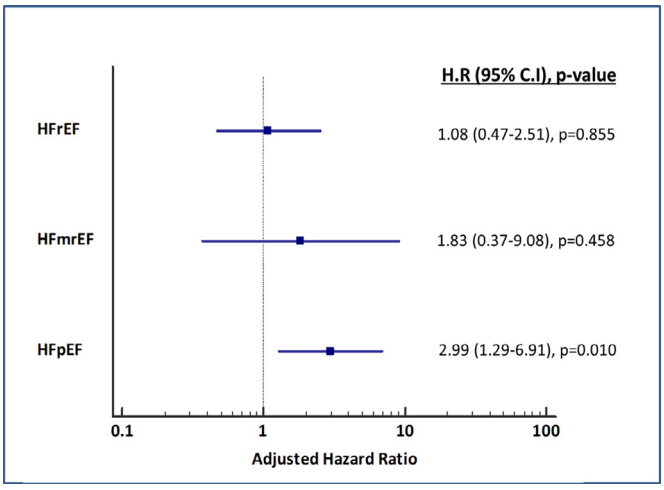

Fig. 2. Multivariable adjusted hazard ratio for 2-year all-cause mortality associated with severe pulmonary hypertension (T3 vs. T1+2, SPAP ≥65 mmhg), according to heart failure subtype. HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction. HR, hazard ratio; CI, confidence interval. * Adjusted for age, sex, heart failure duration, NYHA functional class, creatinine level, diabetes mellitus, coronary artery disease and ischemic cardiomyopathy.

without additional pre-capillary PH. Impaired pulmonary vascular compliance (PCa) and right ventricular-pulmonary artery coupling [reflected by reduced TAPSE/SPAP ratio] suggested more advanced HF, probably identifying these vulnerable HFpEF patients with additional pre-capillary PH.[15,17] A recent multi-center right heart catheterization study of patients with HF showed that for similar levels of PAWP, pulmonary circulation may have been stiffer in patients with HFpEF-PH than patients with HFrEF-PH, leading to higher diastolic pulmonary gradients (DPG).[17] Right heart data and global RV function TAPSE were not routinely collected in all of the centers included in this study. Future studies should assess right heart parameters and TAPSE to clarify the extent of precapillary PH.

Our registry only included patients with HF who already had PH, and we demonstrated that severe PH was associated with increased mortality only in HFpEF. Outcomes in patients with HFmrEF and HFrEF were probably impacted mainly by their reduced cardiac output and the severe PH may only be a marker of their disease severity. In patients with HFpEF, PH may be part of the disease pathophysiology. Specifically, microvascular disease may affect both pulmonary and myocardial vascular beds.

As patients with HFpEF with severe PH have the worst prognosis among all group 2 patients, these patients may be considered as a well-defined population per se, sub-classified as such and accordingly targeted for specific treatments and monitoring of their disease progression.

Limitations

The Registry database includes only demographic, clinical and echocardiographic information. Right heart catheterization was not uniformly performed and therefore was not included in our data analysis. Future studies should use right heart catheterization data to define subgroups of HF patients, in order to develop the best clinical approach for HFpEF with PH patient population. The study was performed in tertiary care centers and therefore, referral and selection bias cannot be excluded.

Conclusions

The mortality of patients with HF-PH is related to the specific combination of preserved EF (>50%) and significant pulmonary pressures (SPAP ≥ 65). Currently, HFpEF patients are included with HF group 2 PH, rather than defined as a sub-class. Since HFpEF patients with PH are likely to have different pathophysiology and worse prognosis, defining these patients as an independent subgroup may be more appropriate for their management and treatment.

Disclosures

The other authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.hrtlng.2019.05.006.

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